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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MORRIS, PATRICIA L	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
12/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,694	RICHTER ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *10-13 and 19-24* is/are withdrawn from consideration.

5)☒ Claim(s) *14-18* is/are allowed.

6)☒ Claim(s) *1-9 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 14-18 and 25-28 are under consideration in this application.

Claims 10-13 and 19-24 remain held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Election/Restrictions

The restriction requirement is deemed sound and hereby maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 and 25-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Turchetta et al.

Applicants assert that the reference of Turchetta et al. is not prior art under 102(e). This is not persuasive because the 102(e) date of Turchetta et al is April 1, 2004 well before applicants' effective filing date of February 28, 2005.

Turchetta et al. teach the instant claimed amorphous salt and the pharmaceutical compositions. Note claim 1 therein. The prior art's pharmaceutical composition comprising risedronate monosodium would be the same as the instant composition comprising the compound, since the amorphous form would no longer exit in solution, or after granulation, compaction or tableting process, as it is well known in the art that such process(es) would lead to

alteration of the form. Note, for example, page 2452 of Threifall. Hence, the claimed amorphous salt and the pharmaceutical compositions are deemed anticipated therefrom.

Applicants assert that the instant amorphous forms are not hydrates. Claims 6-9 have been included in the rejection based on applicants' assertions. Claims 6-9 clearly recite that water is present. Applicants have not provided any objective evidence that the instant amorphous forms differs from the form of Turchetta et al.

Applicants allege that the instant amorphous form has a different X-ray diffraction from the amorphous form of Turchetta et al. However, applicants have failed to provide any objective evidence, *i.e.,* powder X-ray diffraction pattern of the instant amorphous form *vis-a-vis* the prior art amorphous form at the same radiation parameters.

X-ray diffraction pattern alone does not demarcate the identity of two products. It is well recognized in the crystalline solid and amorphous art that sometimes the difference in X-ray diffraction pattern is very minor and must be carefully evaluated before a definitive conclusion is reached. See U.S. Pharmacopia. Further, Davidovich et al. on page 16, states that changes in powder X-ray diffraction often resulted from experimental artifacts rather than polymorphism and that most of these changes were due to particle size/morphology, sample holder/preparation and instrument geometry. Note figure 4.21 on page 118 of Bernstein wherein the same compound shows two different X-ray patterns. Page 272 of Bernstein shows that two identical X-ray patterns, but one is the chemical compound pigment Yellow 14, wherein R is CH_3, while the other is the pigment Yellow 63, R is Cl. Thus, this is an example of identical X-ray displayed by different compounds. The figure on page 273 showed that two X-ray diffraction patterns collected on crystals and recrystals after melting. Although, there are new peaks, the

authors concluded that "it may not be a pure modification", *i.e.,* not a true polymorph. In addition, any X-ray diffraction of an amorphous material is only to show no diffraction or non-crystalline, *i.e.,* a single broad, shallow peak termed an *amorphous halo.* Note pages 578-579 of Nerurkar et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims1-9 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cazer et al. and Turchetta et al. in view of Brittain et al. Threifall, and Muzaffar et al.

Turchetta et al. teach the amorphous form of the instant sodium salt as well as the pharmaceutical compositions, whereas, Cazer et al. teach the crystalline hydrate forms of the claimed compound. Note examples 1 and 2 therein. Brittain et al., Threifall and Muzaffar et al.

teach that compounds can exist in amorphous forms as well as in crystalline forms. Hence the claimed amorphous form as well as its relative selectivity of properties *vis-à-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different crystalline and noncrystalline forms.

Applicants assert that their new amorphous forms are not hydrates. This is not persuasive because Claims 6-10 recite that the forms all contain water from 1 to 10%. It is well understood that the forms recited in claims 1-5 are not hydrates.

The declaration of Jirhan, while interesting, is of little probative value, because it is not commensurate scope with the claims and further compares the closest claimed compound with prior art form because comparisons A and B do not compare the amorphous and crystalline form having similar water content. Claims 8 and 9 recite that the water content can be as high as 10%. Moreover, the declaration fails to include the amorphous form of Turchetta et al. with the anhydrous claimed form. Further, the declaration fails to provide any objective evidence that the instant amorphous forms *vis-à-vis* the crystalline hydrate of Cazer et al. and the amorphous form of Turchetta et al. after processing in the pharmaceutical compositions are any different. Brittain et al. on pages 150-153 state that as hydration or dehydration proceeds, the crystal lattice may expand or contract and as hydration continues, the crystal expand until; the changes are to large to maintain the same crystal. At this point, another crystal structure can result or it may revert to an amorphous material. Page 10 of the Doelker translation, states that amorphous novobiocine acid is transformed into crystalline form, nonresorable, in six months at ambient temperature, a phenomenon that it is possible to combat by adding methyl cellulose. The specification is silent

to any specific carriers that may be employed to combat any conversion of the instant amorphous form. Further, Theifall on page 2452 recites that different amorphous structures may arise from different processes of production.

Claim Rejections - 35 USC § 112

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as well as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks description and enablement as to whether the amorphous form is thermodynamically stable as to provide utility at room temperature for these forms in the compositions and pharmaceutical compositions. The preponderance of evidence in the state-of-the-art indicates that the pharmaceutical formulation field is well aware that amorphous forms when formulated into compositions may undergo transformation thus, the particular form may not be the same form after processing, etc, Hence, compositions containing any particular form cannot be described and enabled with specificity and particularity. For example, page 10 of the Doelker translation, states that the amorphous forms, not thermodynamically stable, in particular have a high solubility, subject to increasing the dissolution rate and the bioavailability. Further, Doelker states that amorphous novobiocine acid is transformed into crystalline form, non-resorable, in six months at ambient temperature, a phenomenon that it is possible to combat by

adding methyl cellulose. The specification is silent to any specific carriers that may be employed to combat any conversion of the instant amorphous form. Muzaffar et al. on pages 63-65 (a)-(h) state that pharmaceutical preparing processes affect polymorphism. Further, Theifall on page 2452 recites that different amorphous structures may arise from different processes of production.

The enablement analysis is applied to the instant case.

The nature of the invention

The nature of the invention is the preparation of amorphous forms of the instant salt and compositions.

State and skill level of the Prior Art and predictability

Although identical in chemical composition, amorphous hydrates can have very different properties. Additionally, hydrates may dehydrate. Lester et al. teach that dehydration of hydrates may easily occur during storage or manufacturing. Amorphous forms tend to convert from less stable to more stable forms. No method exists to predict the forms of a solid compound with any significant certainty. This is why it is important to monitor the amorphous form during manufacture of the drug to see if it persists during manufacture.

The state of the pharmaceutical composition containing polymorphic form art provided per ponderous of evidence that *unless specific and particular* conditions can be obtained, the formulation process would cause polymorphic forms to change.

See :

--Muzaffar et al. p.63-65 (a)-(h) state that pharmaceutical preparing processes affect polymorphism;

--Theifall on. p.2452 recites that different amorphous structures may arise from different processes of production;

> --Doelker et al. abstract "...a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (grinding, tableting, granulations, drying) may also affect secondary properties of the drug, such as compactibility, wetttability, solvent, dissolution rate, bioavailability and even pharmacological, activity."
>
> --Xu ...Influences of environmental conditions such as temperature, humidity, phase transition can cause amorphous materials to transform into crystals during storage and transportation.
>
> --Singhal et al. "..It should be pointed out that a major portion of any formulation effort is the choice of exipients and processes which minimize the chemical instability of the drug…." P.338, left col.

The amount of direction or guidance and the presence or absence of working examples

Figure 4 of the specification only disclose the X-ray diffraction pattern of one compound, i.e., risedronate sodium hydrate in the amorphous form rather than the compositions being claimed in terms of the specific X-ray diffraction patterns. Hydrates often change into other forms during drug manufacture into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the pharmaceutical compositions.

As evidenced by the art of record, it is well known that amorphous forms can convert to other forms.

The breadth of the claims

The breadth of the claims are drawn to the specific amorphous hydrate and non-hydrated forms and in addition to the pharmaceutical compositions.

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the pharmaceuticals

compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

Applicants' allege that the combination of mannitol and microcrystalline cellulose displays exceptionally stability. There is no objective evidence in the specification showing the exceptional stability of the pharmaceutical composition in combination with these two carriers. However, applicants claims' are drawn to all conventional carriers. Per ponderous of evidence in the prior art indicates that for a given form *absent of any description or enablement* from the specification does not *automatically* keep its form in the pharmaceutical composition.

Allowable Subject Matter

Claims 14-18 are allowed.

Conclusion

Claims 1-9 and 25-28 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Patricia L. Morris/
Primary Examiner, Art Unit 1625

plm
December 8, 2008